ON THE DISCRIMINATION OF "PHYSIOLOGICAL" ALBUMINURIA FROM THAT CAUSED BY RENAL DISEASE

AND ON THE MEANS OF CHECKING THE ALBUMINURIA WHERE IT OCCURS INDEPENDENTLY OF SUCH DISEASE

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AND ON THE MEANS OF CHECKING THE ALBUMINURIA WHERE IT OCCURS INDEPENDENTLY OF SUCH DISEASE.

WE propose here to consider in connexion with physiological albuminuria (1) the question as to how it can be discriminated from the albuminuria which is dependent upon organic disease; (2) the question as to the conditions which are favourable to its occurrence; and (3) the question as to how it can be checked.

Introductory.—The idea that the presence or absence of albumin in the urine furnishes a trustworthy criterion of the competence or incompetence of the kidney belongs already to the antiquities of medicine. The question as to whether the renal function is impaired can, as the important work of von Koranyi has made clear, be much more justly adjudicated upon by determining whether the kidney is, or is not, competent to elaborate out of the blood a concentrated saline solution. Taking this as our criterion of renal competency we have recently investigated in a series of cases of physiological albuminuria (*a*) the percentage of salts in the urine and (*b*) the excretory quotient.[1]

Method employed for measuring the salt content of the urine.—One of us working with Kilner showed some time ago[2] that it is possible to substitute for the cryoscopic method introduced by von Koranyi a much simpler method of estimating the salt content of a fluid. The consideration upon which the suggested method was based was the consideration that we can obtain a measurement of the salt content of any fluid by determining the extent to which it must be diluted

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[1] The signification which we attach to this term will appear below.
[2] THE LANCET, April 2nd, 1904, p. 921.

before it completely dissolves a definite quantum of red blood corpuscles. The carrying out of this involved a five-fold series of operations: (1) the preparation of a suitable suspension of red blood corpuscles; (2) the preparation of progressive dilutions of a standard solution of NaCl; (3) the mixture of an appropriate measured volume of each of these dilutions with the suspension of red blood corpuscles, with a view to the determination of the dilution which exerts a complete hæmolytic effect; (4) the preparation of a series of progressive dilutions of the fluid to be tested; and (5) the mixture of an appropriate measured volume of each of these dilutions with the suspension of red blood corpuscles with a view to determining the dilution which exerts a complete hæmolytic effect. We have recently succeeded in dispensing with the first and most lengthy of these operations and have found means to utilise without further preparation for the purposes of the test unaltered blood obtained from a prick in the finger. All that is required for the purposes of the test is to take a single measured volume of this blood and to mix with it in each case two volumes, instead of—as was prescribed in connexion with the corpuscular suspension originally employed—in each case one volume, of the progressive dilutions. An example will serve to show the method of carrying out the test.

(*A*) By the aid of the technique described in THE LANCET[3] two-fold, two and a half-fold, three-fold, three and a half-fold, and four-fold dilutions of a decinormal NaCl solution were made in capillary tubes. Two volumes of each of these dilutions were then measured off and disposed in order upon a glass slide. A puncture was now made in the finger, and a series of five volumes of blood—separated in each case[4] from each other by an air bubble—was aspirated into a throttled capillary pipette. The five single volumes of blood which were thus obtained were now introduced into, and intimately mixed with, the double volumes of diluting fluid already prepared for their reception. The five volumes of diluted blood thus obtained were now drawn up into the capillary pipette, the different dilutions being in each case separated by a bubble of air. On examining the contents of the tube under oblique illumination it was now clearly seen that no hæmolysis had taken place in the sample of blood which had been mixed with the $\frac{N}{20}$ and $\frac{N}{25}$ solution; that incomplete hæmolysis had taken place in the sample which had been mixed with the $\frac{N}{30}$ solution; and that complete hæmolysis had taken place in the samples which had been mixed with the $\frac{N}{35}$ and all the higher dilutions. It was clear from this result that a solution which produces complete hæmolysis when mixed with the particular blood here employed in the proportion of two volumes of the diluting solution to one volume of the blood possesses a salt content equivalent to $\frac{N}{35}$.

(*B*) A urine derived from a healthy man, who had recently emptied his bladder and who had not ingested any fluid for some hours before, was now taken in hand. Two-fold, four-fold, eight-fold, and 16-fold dilutions were made of this urine with distilled water and in each case two volumes of these dilutions were mixed with one volume of blood

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[3] THE LANCET, July 5th, 1902, p. 11.
[4] Figured in THE LANCET of Jan. 23rd, 1904, Figs. 10–13, p. 217.

TABLE I.—GIVING SUMMARY OF THE RESULTS OF EXAMINATION OF THE BLOOD AND THE URINE IN EIGHT CASES OF PHYSIOLOGICAL ALBUMINURIA.

No. of case.	Initials, age, and date.	Clinical data.	General character of the urine.	Excretory efficiency of kidneys as determined by the method of hæmolysis.		
				Hæmosozic value of the serum.	Hæmosozic value of the urine.	Excretory quotient.
1	A. B., aged 19 years. March 23rd, 1905.	The patient had had no illness predisposing to nephritis. He had always been well and strong and was so at the time of examination. The albumin was discovered when the patient went up for medical examination. There were no signs of nephritis, either renal or cardiac, other than the presence of albumin in the urine.	Good colour; acid; specific gravity, 1018; albumin ¼ by boiling, absent in early morning specimen, present in afternoon specimen.	= 1·75 per cent. NaCl.	= 3·90 per cent. NaCl.	2·2
2	C. D., aged 21 years, a medical student. March 24th, 1905.	Similar to Case 1. Albumin was discovered accidentally.	Good colour; acid; specific gravity, 1022; albumin, a pronounced trace, absent in early morning specimen, present in afternoon specimens.	March 24th, 1905: = 1·17 per cent. NaCl.	= 2·34 per cent. NaCl.	2·0
				June 7th, 1905: = 0·67 per cent. NaCl.	= 1·74 per cent. NaCl.	2·6
3	E. F., aged 28 years. April 14th, 1905.	Similar to Cases 1 and 2, except in the respect that the patient is an extremely nervous subject. Albumin was discovered accidentally.	Good colour; acid; specific gravity, 1018; albumin, 0·04 per cent. (by Esbach), absent in morning specimen, present in afternoon specimens.	March 14th, 1905: = 1·36 per cent. NaCl.	= 2·73 per cent. NaCl.	2·0
				June 7th, 1904: = 0·96 per cent. NaCl.	= 3·3 per cent. NaCl.	3·4
4	G. H.,* aged 15 years. May 11th, 1905.	Similar to Cases 1, 2, and 3. Albumin was discovered when the patient presented himself for medical examination.	Good colour; acid; specific gravity, 1018; albumin, 0·15 per cent. (by Esbach), absent in morning specimen, present in afternoon specimens.	= 1·56 per cent. NaCl.	= 3·12 per cent. NaCl.	2·0
5	I. J., aged 12 years. April 4th, 1904.	Puffiness developing beneath the eyes led to examination of the urine and detection of albumin. Albuminuria was notably increased by active exercise. The patient was robust and in perfect health.	Albumin, a pronounced trace present in specimen collected some hours after rising.	= 1·0	= 2·0	2·0
6	K. L., aged 45 years. March 22nd, 1904.	The patient, a robust artisan, came to hospital suffering from giant urticaria and recent hydrocele.	Albumin present; one-eighth by boiling.	= 0·7	= 1·8	2·5
7	M. N., aged 17 years. March 22nd, 1904.	Similar to Case 1. Albumin present, especially after severe exercise (shooting).	Albumin, a pronounced trace, present in specimen collected some hours after rising.	= 0·835	= 1·87	2·2
8	O. P., aged 55 years.	Similar to Case 1. No atheroma or increased arterial tension.	Colour good; specific gravity 1018; no casts; no blood; quantity normal; albumin absent in early morning specimens; generally a trace of albumin in specimen collected a few hours after rising; a pronounced trace practically always after active exercise.	—	= 1·94	—

* We are indebted to Dr. Lewis A. Smith of the London Hospital for permission to make observations on this case.

obtained from the same source as before. It was now found that no hæmolysis took place in the samples of blood which had been mixed with the two- and four-fold dilutions of the urine, a trace only of hæmolysis in the eight-fold dilution, while the 16-fold dilution showed complete hæmolysis. In view of this result a 12-fold dilution of the urine was made by mixing two volumes of the eight-fold dilution which was ready to hand with one volume of distilled water. On mixing two volumes of this 12-fold dilution with one volume of blood only incomplete hæmolysis was obtained. It followed from these results that the salt content of the 16-fold dilution of urine was exactly equivalent to that of the 35-fold dilution of normal NaCl solution employed in (*A*). A simple arithmetical calulation now showed that a $\frac{N}{35}$ solution of NaCl—equivalent as it is to a 5·85 per cent. solution ÷ 35—contains 0·167 per cent. of NaCl; and that a urine whose 16-fold dilution contains the equivalent of this percentage of salt, contains in its undiluted condition the equivalent of 2·67 per cent. of NaCl.

The whole calculation may perhaps most conveniently be thrown into the following form.

$$\frac{U}{16} = \frac{N}{35} = \frac{5{\cdot}85\%}{35} = 0{\cdot}167\%.$$
$$U = 0{\cdot}167\% \times 16 = 2{\cdot}67\%.$$

Method employed for the determination of the excretory quotient.—The "excretory quotient" was in the paper already referred to[5] defined as the expression for the efficacy of the kidney which is obtained by dividing the salt content of a patient's blood into the salt content of his urine. It might, in relation to the limitations associated with the hæmolytic method and to the circumstance that this method takes cognisance not alone of the salt content but also of any other element in a fluid which counteracts hæmolysis, have been more accurately defined as the expression for the efficacy of the kidney which is obtained by dividing the hæmosozic[6] value of a patient's serum into the hæmosozic value of the urine secreted from that blood fluid. The excretory quotient is elicited by collecting from a patient who has just emptied his bladder a sample of blood and as soon afterwards as may be practicable a sample of urine. Progressive dilutions are made of the serum and urine thus obtained and each of these dilutions is mixed by the technique described above with blood in the proportion of two volumes of diluting fluid to one volume of blood. The excretory quotient is then obtained in accordance with the formula—

$$\frac{\text{Minimum dilution of the urine which effects complete hæmolysis.}}{\text{Minimum dilution of the serum which effects complete hæmolysis.}}$$

Discrimination of "physiological albuminuria" from the albuminuria of organic disease by the aid of the methods described above.—It will be seen on referring to Table I., which summarises the results of examinations of the blood

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[5] THE LANCET, April 2nd, 1904, p. 921.

[6] The term "hæmosozic" here applied to those constituents of a fluid which preserve the red blood corpuscles from solution is borrowed rom Armand Ruffer.

and urine which we have carried out on a series of seven typical cases of physiological albuminuria and in one further case which would seem also to fall into that category, that the excretory quotient is in each case high and that the salt content of the urine has approximated to or exceeded 2 per cent. NaCl, while it has in some cases largely surpassed that figure. These results, which are fully equal to any obtained upon healthy persons, contrast in a very marked manner with those obtained in connexion with renal disease and thus furnish what is in our judgment conclusive evidence that the renal function is in cases of "physiological albuminuria" entirely unimpaired.

Conditions which are favourable to the transudation of lymph into the urinary tubules.—When we reconsider the pathology of "physiological albuminuria" in the light of the data incorporated in Table I. we are led almost inevitably to the conclusion that we have to deal in this condition with a transudation of lymph into intact urinary tubules. This inference wins support from the consideration that the conditions which are favourable to the occurrence of serous

TABLE II.—*Showing the Restraining Influence which is Exerted by Calcium Salts on the Output of Albumin in Physiological Albuminuria.*

—	Period at which observation was made.	Blood-coagulation time.	Maximum concentration of oxalate of ammonium required for decalcification of an equal volume of blood.	Quantity of albumin in the urine and method employed for precipitation of albumin.
A. B. ...	Before the administration of calcium salts.	1 min. 40 secs.	1 in 1500.	¼ volume, boiling.
	60 grains of calcium lactate administered.			
	One and a half hours after the administration of calcium salts.	1 min. 20 secs.	1 in 1000.	½th volume, boiling.
	Two 20 grain doses of calcium lactate administered.			
	24 hours after the first administration of calcium salts.	1 min. 20 secs.	1 in 1200.	None.
C. D. ...	Before the administration of calcium salts.	1 min. 25 secs.	1 in 1350.	Pronounced trace.
	60 grains of calcium lactate administered.			
	One hour after the administration of calcium salts.	1 min.	1 in 1200.	None.

—	Period at which observation was made.	Blood-coagulation time.	Maximum concentration of oxalate of ammonium required for decalcification of an equal volume of blood.	Quantity of albumin in the urine and method employed for precipitation of albumin.
E. F. ...	Before the administration of calcium salts.	—	1 in 1350.	0·04 per cent., Esbach.
	60 grains of calcium lactate administered.			
	One hour and three-quarters after the administration of calcium salts.	—	1 in 1200.	Slight haze, boiling.
	20 grains of calcium lactate administered three times a day.			
	Six days after the first administration of calcium salts.	—	—	Trace.
	20 grains of calcium lactate administered three times a day.			
	19 days after the first administration of calcium salts.	—	1 in 800.	None.
G. H. ...	Before the administration of calcium salts.	1 min. 55 secs.	—	0·15 per cent., Esbach.
	60 grains of calcium lactate administered.			
	Two hours after the administration of calcium salts.	1 min. 20 secs.	—	0·05 per cent. Esbach.
	24 hours after the administration of calcium salts.	—	—	None.
K. L. ...	Before the administration of calcium salts. While the patient was suffering from giant urticaria.	—	1 in 1200.	$\frac{1}{8}$th volume, boiling.
	20 grains of calcium chloride administered three times a day.			
	Four days after the first administration of calcium salts, the urticaria having completely disappeared.	—	1 in 750.	None.
O. P. ...	Before the administration of calcium salts and after walking several miles.	2 mins. 15 secs.	1 in 1000.	Definite trace.
	24 hours' interval; then the ingestion of 60 grains of calcium chloride.			
	After the administration of calcium salts followed by same walk as before.	1 min. 40 secs.	—	None.

hæmorrhage in general—to wit, increased hydrostatic pressure in the capillaries of a particular region, and diminished blood coagulability—are favourable also to the appearance of albumin in the urine in the cases we have here in view. We may recall to mind in this connexion that the appearance of albumin in the urine in physiological albuminuria is influenced by active exercise, by nervous disturbances, and by the assumption of the erect posture; and we may note that under all of these conditions the hydrostatic pressure in the renal capillaries would be increased. We may further in this connexion take cognisance of the fact that a condition of diminished blood coagulability was found in many of our cases of physiological albuminuria; and that the output of albumin in cases of physiological albuminuria can, as is shown in the next section of this paper, be restrained by increasing the coagulability of the blood. It must be left for future experiment to determine whether in physiological albuminuria, as in urticaria, the exudation can be increased by the ingestion of decalcifying and lymphagogic agents—we have in view here in particular those lymphagogic agents which are contained in shell-fish, crustacea, and strawberries. Pending the carrying out of such experiments it is of interest to note that in one of the cases which we have included in Table I. albuminuria was associated with giant urticaria and recent hydrocele, while in another case occasional puffiness under the eyes was a marked feature.

Observations on the possibility of restraining the output of albumin in physiological albuminuria by increasing the coagulability of the blood.—On following up the line of thought which has been indicated in the foregoing it occurred to us that it ought to be possible to check the excretion of albumin in physiological albuminuria by increasing the coagulability of the blood by the aid of calcium salt. The data set forth in Table II. show that this line of treatment which is effective in many cases of chilblains and urticaria, in weeping eczema, and also in many cases of general œdema due to Bright's disease, is effective also in the case of physiological albuminuria.

In connexion with the results given in Table II. and those set down in previous papers[7] with regard to the effect of a milk dietary upon the coagulability of the blood and its content in lime salts it is interesting to one of us to recall the medical history of one of his pupils who had passed into the Indian Medical Service. This officer, who was the son of a medical man, related that both he and a succession of his brothers had on reaching the period of early adolescence—i.e., the period at which lime salts would be taken out of the blood in connexion with the processes of growth—developed

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[7] Transactions of the Royal Medical and Chirurgical Society, vol. lxxxvi., 1903; and THE LANCET, Oct. 14th, 1905, p. 1096.

TABLE III.—SHOWING THAT THE ALBUMINURIA OF RENAL DISEASE IS NOT ABOLISHED BY THE EXHIBITION OF CALCIUM SALTS.

No. of case.	Initials, age, and date.	Clinical data.	General character of the urine.	Dates of examination.	Excretory efficiency as determined by the method of hæmolysis.			Effect of the administration of calcium lactate.
					Hæmosozic value of the blood serum.	Hæmosozic value of the urine.	Excretory quotient.	
1	C. W., aged 15 years. April 18th, 1905.	Patient has been ill for at least nine months and presents typical symptoms and signs of parenchymatous nephritis—œdema, headaches, thickened arteries, increased arterial tension, and hypertrophied heart.	Smoky; acid; specific gravity, 1016; Albumin; granular epithelial blood casts and blood; about 25 ounces per diem.	Nov. 18th, 1904. Nov. 19th, 1904. Nov. 29th, 1904.	= 1·17 per cent. NaCl. = 1·56 per cent. NaCl. = 0·97 per cent. NaCl.	= 1·17 per cent. NaCl. = 0·78 per cent. NaCl. = 0 585 per cent. NaCl.	1·0 0·5 0 6	Jan. 1st, 1905.—*Before the administration of calcium salts:* coagulation time of blood, 1 minute 50 seconds; minimum concentration of ammonium oxalate required for decalcification, 1 in 1750; albumin, 1·6 per cent. by Esbach. 40 grains of calcium lactate administered. *2¼ hours after the administration of calcium salts:* coagulation time of blood, 1 minute; minimum concentration of ammonium oxalate required for decalcification, 1 in 1200; albumin, 0·9 per cent. by Esbach.
2	T. S., aged 17 years. May 3rd, 1905.	Patient is the subject of a typical parenchymatous nephritis following exposure to cold and wet. Signs and symptoms as in Case 1 and in addition ascites.	As in Case 1; specific gravity, 1012; albumin; from 20 to 30 ounces per diem.	Nov. 16th, 1904. Nov. 20th, 1904. Nov. 29th, 1904. Dec. 12th, 1904.	= 0·82 per cent. NaCl. = 0·78 per cent. NaCl. = 0·97 per cent. NaCl. = 0·97 per cent. NaCl.	= 0 819 per cent. NaCl = 0 78 per cent. NaCl. = 0·78 per cent. NaCl. = 0·78 per cent. NaCl.	1·0 1·0 0·8 0·8	Jan. 1st, 1905.—*Before the administration of calcium salts:* coagulation time of blood, 1 minute 45 seconds; albumin §ths by boiling. 60 grains of calcium lactate administered. *Two and a half hours after the administration of calcium salts:* coagulation time of blood, 1 minute 25 seconds; albumin §ths by boiling.
3	W. W., aged 49 years, shipwright. May 5th, 1905.	At least one year's duration. Œdema of the eyelids, the conjunctiva, and the legs; severe headaches, anæmia, loss of appetite, thickened arteries, high arterial tension, and hypertrophied heart.	Colour, pale; specific gravity, 1010; acid; albumin; hyaline casts; quantity, from 80 to 100 ounces per diem.	Dec. 5th, 1905.	= 1·36 per cent. NaCl.	= 1·36 per cent. NaCl.	1 0	Jan. 1st, 1905.—*Before the administration of calcium salts:* coagulation time of blood, 30 seconds; concentration of ammonium oxalate required for decalcification of blood over 1 in 800; albumin, ½ by boiling; 0 68 per cent. by Esbach. 60 grains of calcium lactate administered. *Two and a half hours after the administration of calcium salts:* coagulation time of blood, 25 seconds; concentration of ammonium oxalate required for decalcification of blood over 1 in 600; albumin, ½ by boiling; 0·76 per cent. by Esbach.
4	A. B., aged 21 years.	Albuminuria associated with a coli infection of the urinary passages which has persisted for years.	Turbid with bacteria; no casts; much bladder epithelium; some polynuclear white blood corpuscles. Albumin; quantity normal.	Feb. 6th, 1905.	= 0·6 per cent. NaCl.	= 0·85 per cent. NaCl.	1·4	Feb. 6th, 1905.—*Before the administration of calcium salts:* coagulation time, 1 minute 50 seconds; minimum concentration of oxalate of ammonium required for decalcification of blood, 1 in 1000; albumin, 0·17 per cent. 60 grains of calcium lactate administered. *45 minutes after administration of calcium salts:* coagulation time, 25 seconds; minimum concentration of oxalate of ammonium required for decalcification of blood, 1 in 750; albumin, 0·66 per cent.

albuminuria which had in each case been permanently arrested by rest in bed combined with a dietary of milk.[8]

On the possibility of discriminating the albuminuria which occurs independently of renal disease from the albuminuria which is due to such disease by noting the effect produced upon the output of albumin by the exhibition of calcium salts.—Having found, as has been shown above, a method by which physiological albuminuria can be abolished the next point which suggested itself for investigation was the question as to whether calcium salts were competent also to abolish the excretion of albumin in albuminuria dependent upon renal disease. The data set forth in Table III. furnish the answer to this question. It will be seen that in spite of the fact that the coagulability of the blood was in each case increased the output of albumin was not diminished. We have here, as reflection will show, a fact which may with advantage be exploited in the differential diagnosis of albuminuria dependent on kidney disease from physiological albuminuria or, as the case may be, in the determination of the question as to whether albuminuria is or is not in part referable to a simple transudation.

Conclusions.—We venture to suggest, in view of the observations which are set forth in this paper, that it will no longer be justifiable to take, in connexion with examination for insurance or for entry into the public services, the serious view of physiological albuminuria which has hitherto been taken by most clinicians. Where it is found that a patient possesses a normal excretory quotient, and that his albuminuria can be abolished by diminishing the hydrostatic pressure on the renal capillaries and by increasing the coagulability of the blood, there is, we submit, every reason to conclude that the kidney is free from organic disease and that life is no more endangered than it would be if the patient were the subject of urticaria.

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[8] We learn from a paper by Dr. Clement Dukes (Brit. Med. Jour., Oct. 7th, 1905) published while this was in the press that he has seen physiological albuminuria disappear under a regimen of milk even apart from rest in bed. Such results would be in all points comparable to those in Table II. above obtained by the exhibition of calcium salts.

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